REMARKS

Claims 1-3, 7-16, 29 and 30 are pending in this application. No claims are added or deleted. Therefore, claims 1-3, 7-16, 29 and 30 are pending for consideration.

I. Claim Rejections - 35 USC § 103

Claims 1-3, 7-16, and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Szyf *et al.* (WO 99/24583, applicants' citation No. A01) in view of Monia *et al.* (US 6,008,048) and Deeley *et al.* (US 6,001,563).

According to the Examiner, the claims are drawn to a combination product comprising at least one MBD2 antisense oligonucleotide and bleomycin, wherein the antisense oligonucleotide is administered about 30 minutes after the injection of the bleomycin, and wherein the antisense oligonucleotide is targeted to SEQ ID NO: 1.

The Examiner further states that Szyf *et al.* teach SEQ ID NO:5, which is identical to instantly claimed SEQ ID NO: 1 and teach that demethylase inhibitors can be used as anticancer agents. The Examiner further states, among other things, that Szyf *et al.* teach that such demethylase inhibitors include antisense oligonucleotides or ribozymes targeted to the demethylase cDNA sequence comprising SEQ ID NO:5 (pages 5-7). The Examiner admits that Szyf *et al.* do not teach a combination product comprising a demethylase antisense oligonucleotide and bleomycin, nor do they teach a method of delivering the combination product.

The Examiner cites Monia *et al.* for allegedly teaching pharmaceutical compositions comprising one or more antisense oligonucleotides and one or

more chemotherapeutic agents including bleomycin (column 24, lines 4-10). According to the Examiner, Monia teaches that the antisense oligonucleotides and chemotherapeutic agents can be used simultaneously or sequentially (column 24, lines 28-29). The Examiner further asserts that Monia teaches the formulation of therapeutic compositions and their subsequent administration via various routes is within the skill of those in the art (column 24, lines 38-63), that pharmaceutical compositions comprising antisense oligonucleotides can be formulated in various ways, and asserts that the techniques of making pharmaceutical compositions are well known in the pharmaceutical industry (columns 11-12).

The Examiner cites Deeley *et al.* for allegedly teaching that antisense oligonucleotides can be produced from an expression vector in cells (column 14, lines 53-65; columns 15-17 and 28). According the Examiner, Deeley teach that the expression vector containing an antisense oligonucleotide can be introduced into mammalian cells by various means including electroporation and microinjection (column 17, lines 26-34) and teach pharmaceutical compositions suitable for injectable use (column 24).

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the antisense oligonucleotide targeted to SEQ ID NO:5 of Szyf *et al.* with a chemotherapeutic agent bleomycin of Monia *et al.* and to express the antisense oligonucleotide of Szyf *et al.* from an expression vector for electroporation or microinjection as taught by Deeley.

The Examiner explains that one of ordinary skill in the art would have been motivated to combine the teachings of the prior art with a reasonable expectation of success because the full length target gene cDNA sequence

(MBD2 or demethylase) was known in the art, which is disclosed as SEQ ID NO:5 in the Szyf *et al.'s* reference, and because MBD2 was known to be over expressed in several cancer cells and therefore reducing the expression of MBD2 by virtue of antisense oligonucleotides was suggested to reduce tumorigenesis by Szyf *et al.* (pages 41, 43). The Examiner further asserts that a combination product comprising one or more antisense oligonucleotides and one or more chemotherapeutic agents, administered either together or separately, was known to be used as an anticancer agent in the art as taught by Monia *et al.* (column 24). Since Szyf *et al.* expressly teach that an antiMBD2 antisense oligonucleotide can be an anticancer agent (pages 5-7), and since a combination product comprising antisense oligonucleotides and chemotherapeutic agents was known in the art as of the earliest filing date sought in the instant application, one of ordinary skill in the art would have been motivated to combine the antisense anticancer agent targeted to the instantly claimed SEQ ID NO:1 as taught by Szyf *et al.* with one or more chemotherapeutic agents for additive or synergistic effect of reducing tumorigenesis. Moreover, according to the Examiner, the skilled artisan would have been motivated to construct a vector that expresses the anti-MBD2 antisense oligonucleotide with a reasonable expectation of success because Deeley *et al.* teach that antisense oligonucleotides can be produced from an expression vector in mammalian cells and that vectors comprising antisense oligonucleotides can be introduced into mammalian cells via electroporation or microinjection.

The Examiner also cites *In re Kerkhoven,* wherein the court expressed the following:

"It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose... [T]he idea of combining them

flows logically from their having been individually taught in the prior art." *In re Kerkhoven* 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980).

The Examiner concludes that since both antisense and bleomycin were recognized in the art as anticancer therapeutic agents, it would have been *prima facie* obvious to combine them for treatment of cancer with a reasonable expectation of success. See also MPEP 2144.06.

Applicants respectfully traverse this rejection. The Examiner acknowledges that Szyf *et al.* teach nothing about combining the antisense oligonucleotide of DNA demethylase with any agent for use in antitumor chemotherapy for simultaneous or separate use for the treatment of proliferative and inflammatory diseases. The Examiner further admits that Monia teaches nothing about an antisense oligonucleotide of MBD2 demethylase. Rather Monia teaches antisense compounds for modulating the expression of EGR-1, also known as early growth response 1, which is a transcriptional activator. Also, Monia generally mentions using such antisense compounds with chemotherapeutic agents. Deeley is cited for generally supporting the notion that expression vectors can be used to produce antisense oligonucleotides and that electroporation can be used to introduce nucleic acids into mammalian cells.

In fact, none of these three references suggest their combination. Such combination is based upon knowing the invention, which cannot support a *prima facie* case of obviousness. The Examiner's case appears to be that because others have suggested antisense oligonucleotides with other chemotherapeutic agents, and tools were available for use, one of skill in the art would have found applicants' invention obvious. Applicants argue that these general teachings fall short of leading the skilled artisan in a direct path toward the claimed invention as is required to support a *prima facie* case of obviousness. Additionally, applicants

dispute the Examiner's conclusion that there would have been an expectation of success because such conclusion ignores that nature of the art of the invention, which is highly unpredictable. In view of these remarks, applicants respectfully request the Examiner to reconsider and withdraw the rejection for prima facie obviousness.

Applicants do not agree that the claimed invention is *prima facie* obvious in view of the above comments. However, applicants also point out that nothing in the cited art alone or in combination would have suggested the results achieved with the claimed combination. At page 3, lines 25-35, applicants disclose the powerful synergistic effect using the claimed combination in the treatment of tumors. Such synergistic effect was an unexpected result. Any *prima facie* case of obviousness is rebutted by such results. Withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

In light of the above arguments, applicants respectfully request that all rejections and objections be withdrawn and that a timely Notice of Allowance should be issued in this application. Should the Examiner have any questions, the Examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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